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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,396	03/01/2004	Shumin Yang	IM-1-C1-PUS-1	3337

26949 7590 09/13/2004

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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/790,396	YANG ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40 – 52 and 60 – 64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-45, 47-48, 51-52, 60, 62, and 63* is/are rejected.

7)☒ Claim(s) *46,49,50,61 and 64* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 07/22/2004, is acknowledged.

2. Applicant's election with traverse of Group I, claims 40 – 52 (now claims 40 – 52 and 60 – 64), drawn to canine B7-2 proteins and compositions thereof, in the reply filed on 07/22/2004 is acknowledged.

The traversal is on the ground(s) that as the canine (Group I) and feline (Group II) B7-2 sequences are closely related, a search for the subject matter of Group I would be sufficient to enable the examination of the claims of group II without constituting an undue burden for the Examiner. This is not found persuasive because the proteins of Groups I and II are distinct and divergent, and the search for the their sequences is not co-extensive, thus placing an undue burden upon the Examiner. Further, a prior art search also requires a literature search. It is an undue burden on the Examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

It is noted that non-elected claims 53 – 59 have been cancelled.

3. Claims 40 – 52 and 60 – 64, as they read on canine B7-2 proteins and compositions thereof, are under consideration in the instant application.

It is noted that sequences pertaining to canine B7-2 proteins under consideration are SEQ ID NOS 7 and 17 (protein), SEQ ID NOS 9 and 19 (nucleotide), and SEQ ID NOS 10 and 20 (complementary nucleotide).

4. The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

5. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Provisional application 60/078,765 appears to provide adequate support for claims 40 – 42, 44, 46, 47, 49 – 52, 61, 62, and 64, as they read on the elected invention of canine B7-2 proteins and compositions thereof.

Claims 43, 45, 48, 60, and 63 may not have the benefit under 35 U.S.C. 119(e) of the filing date of provisional application 60/078,765. Specifically, support for the functional limitation of "capable of binding a CTLA4 or CD28 protein or capable of stimulating T cells" is absent from the provisional application.

Application 09/062,597, to which the instant Application claims priority, appears to provide support for the limitation of "binding CTLA4 or CD28," but not the limitation of "stimulating T cells."

Thus the effective filing date of claims 43, 45, 48, 60, and 63 is considered to be the filing date of PCT/US99/06187, i.e. 03/19/1999.

6. The specification on page 1, paragraph 1 should be amended to reflect the status of the parent application USSN 09/062597.

The filing date of parent application 09/646,561, disclosed on page 1 line 2 (as amended) is not consistent with PTO records. The filing date is listed as 02/01/2001, whereas the PTO records indicate a filing date of 09/19/2000. Appropriate correction or clarification is required.

7. The oath or declaration is defective because: signature of co-inventor Gek-Kee Sim is absent.

It is noted that the Applicant has provided a copy of Decision on Renewed Petition under 37 CFR 1.47(a), of 11/29/2001, "to accept the application without the signature of co-inventor Gek-Kee Sim," pertaining to parent application 09/646,561, to which the instant application claims priority. To complete the record of the instant application, the Applicant is required to provide a copy of the Petition under 37 CFR 1.47(a) filed with Application 09/646,561, and invited to clarify the record of the instant application with regard to inability to reach the missing joint inventor after diligent efforts.

8. It is noted that the Oath or Declaration list two Inventors, Shumin Yang and Gek-Kee Sim, while the IDS (filed 05/17/2004) and the Application Transmittal sheet (03/01/2004) list an additional Inventor, Karen S. Sellins. The Applicants are invited to clarify the record with regard to inventorship of the instant application.

9. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

10. The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

11. Applicant's IDS, filed 05/17/2004, is acknowledged. The date of document C41 has been filled in by the Examiner.

The IDS states that copies of documents listed on instant form PTO-1449 which were previously submitted with parent application 09/646,561 are not being provided. However, it appears that only three of the 43 references listed on the instant PTO-1449 have been cited in previous application 09/646,561 (IDS filed 06/24/2002).

Consequently, the instant citations which were not listed on IDS filed 06/24/002 in application 09/646,561 have been crossed out. Applicant is invited to submit missing references to complete the instant file.

12. The use of trademarks such as MacVector™ (page 26) and Lipofectamine and OptiMEM (page 59) has been noted in this application. Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

13. Claims 50, 60, 61, and 64 are objected to because of the following informalities: the phrases "consists an amino acid" or "consisting a nucleic acid" apparently lack the intended preposition "of." Appropriate correction is required.

Claim 41 is objected to because of the following informalities: in the recitation of "a portion of the transmembrane domains" singular form of the word "domain" appears to have been intended. Appropriate correction or clarification is required.

Applicant is advised that should claim 50 be found allowable, claim 64 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

14. The following is a quotation of the ***second paragraph of 35 U.S.C. 112.***

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 42, 43, and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) The "hybridization under stringent conditions," recited in claim 42, is indefinite in that it does not specify the metes and bounds of the hybridization conditions. Although the specification discloses on pages 14 – 17 general parameters for calculating such conditions, in the absence of a clear definition of the metes and bounds of this phrase it is unclear which conditions are actually claimed.

It is suggested that Applicant amend claim 42 to recite a specific set of hybridization and wash conditions to overcome this rejection.

(B) Claim 52 recites the limitation "composition of claim 50." There is insufficient antecedent basis for this limitation in base claim 50, as claim 50 recites an isolated protein. It appears that claim 52 was intended to depend on claim 51.

Foe examination purposes, claim 52 is assumed to depend on claim 51.

(C) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

16. The following is a quotation of the ***first paragraph of 35 U.S.C. 112:***

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 47 and 62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection**.

The limitation "an isolated protein of at least about 50 amino acids in length, wherein said protein comprises an at least 50 contiguous amino acid region identical in sequence to a 50 contiguous amino acid region" in claims 47 and 62 represents a departure from the specification and the claims as originally filed, and Applicant has not pointed out where the support comes from.

Applicant is required to cancel the New Matter in the response to this Office Action.

Alternatively, Applicant is invited to clearly point out the written support for the instant limitations.

18. Claims 40 – 45, 47 – 48, 51, 52, 60, and 62 – 63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated protein comprising an amino acid sequence set forth in SEQ ID NOS: 7 and 17, and an isolated protein encoded by a nucleic acid molecule comprising a sequence set fort in SEQ ID NOS: 9 and 19, which, when administered to canines, regulates T-cell mediated immune responses in canines, ***does not reasonably provide enablement for a protein which:***

(A) constitutes "any homolog" of B7-2, such as containing modifications in which amino acids have been deleted, inserted, inverted, substituted or derivatized, or arise through natural allelic variation or alternative RNA splicing (claims 40, 41, and 51, directed to a B7 protein as read in light of the specification on page 10, paragraph 2, and page 11, paragraph 2);

(B) is encoded by a nucleic acid molecule of at least 150 nucleotides in length that hybridizes under stringent conditions with a nucleic acid of SEQ ID NO:10 or 20 (claims 42 – 43);

(C) is encoded by a nucleic acid molecule comprising at least 150 contiguous nucleotide region identical to a region of SEQ ID NO:9 or 19 (claim 44);

(D) is encoded by a nucleic acid molecule comprising sequence at least 95% identical to SEQ ID NO:9 or 19 (claims 45 and 60);

(E) is at least about 50 amino acids in length, and comprises an at least 50 contiguous amino acid region identical in sequence to SEQ ID NO:7 or 17 (claims 47 and 62); or

(F) comprises an amino acid sequence at least about 85% identical to SEQ ID NO:7 or 17 (claims 48 and 63),

(G) a polypeptide which, when administered to an animal, regulates T-cell mediated immune responses in said animal (claim 51).

The specification does not provide a sufficient enabling description of the claimed invention.

The specification discloses two nucleic acid sequences SEQ ID NOS:9 and 19 (and complements SEQ ID NOS:10 and 20), encoding canine B7-2 polypeptides (SEQ ID NOS:7 and 17) with a disclosed activity of binding CTLA4 and CD28 proteins and stimulating T cells in dogs, cats, horses and humans (page 10 and page 49). The instant claims encompass in their breadth *any* homolog or a polypeptide of 50 amino acids, or a polypeptide with at least 85% identity to canine B7-2, or *any* polypeptide encoded by a nucleic acid that hybridizes to SEQ ID NO:10 or 20, including those that comprise a fragment thereof, which, when administered to *any* animal will regulate T-cell mediated immune response.

(A) Modifications, allelic variants and splice variants.

The instant claim language encompasses modifications of the disclosed sequences, such as amino acid substitutions, deletions, and insertions (claim 40, read in light of the specification on page 10, paragraph 2 and page 11, paragraph 2). Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al (J Cell Biol. 1990, Vol. 111, pp. 2129-2138; in particular, pages 2132 - 2133) show that a conservative replacement of a single "lysine" reside at position 132 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol. 1988, Vol. 8, pp. 1247-1252; in particular, page 1250 and Table 1) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Also, Metzler et al. (Nature Structural Biol. 1997, Vol. 4, pp. 527-531; in particular, pages 728 – 729 and Table 2) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al.: Science, 1990, Vol. 247, pp. 1306-1310; in particular, page 1306, col. 2).

Thus the recitation of a range of possible protein sequence modifications, in the absence of guidance as to the specific nature of modifications resulting in a functional polypeptide, does not allow the skilled artisan to make and use the nucleic acids encoding the variant polypeptides commensurate in scope with the instant claims without undue experimentation.

The term "allelic variants" encompasses one of several possible naturally occurring alternate forms of a gene occupying a given locus on a chromosome of an organism or a population of organisms. Similarly, a "splice variant" is a reference to a nucleic acid molecule, usually RNA, which is generated by alternative processing of intron sequences in an RNA transcript of B7-L polypeptide. Applicant has not provided sufficient biochemical information (e.g. nucleic acid sequences, etc.) that distinctly identifies the *allelic variants or splice variants* of SEQ ID NOS:9 or 19, other than those set forth in SEQ ID NOS:9 and 19.

It is not sufficient to define a specificity by its principal biological activity or structure, e.g. for allelic variants or splice variants of SEQ ID NOS:9 and 19, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. The specification appears to provide insufficient guidance on the structure of allelic variants or splice variants of SEQ ID NOS:9 or 19.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of allelic variants or splice variants of SEQ ID NOS:9 and 19. The scope of the claims must bear a reasonable correlation with the scope of enablement. The specification does not provide for sufficient enablement for allelic variants or splice variants of SEQ ID NOS:9 or 19 other than those defined by SEQ ID NOS:9 and 19.

(B) Hybridization.

Similarly, the fact that two nucleic acid sequences will hybridize under stringent conditions (claim 42) does not in and of itself require that the two sequences share any functional activity. It was well known in the art at the time the invention was made that hybridization could occur between two sequence based upon short stretches of 100% identity. Thus a great deal of sequence variability *with respect to the full-length nucleic acid* is possible. Finally, hybridization under conditions other than high stringency would be expected to permit a great deal of variation between the two hybridizing sequences, making it even more unpredictable that the two sequences would share the same function.

Thus hybridization language or limitations regarding either the hybridization conditions or the sequence length over which the hybridization takes place, do not allow the skilled artisan to make and use the proteins encoded by the hybridizing nucleic acids commensurate in scope with the instant claims without undue experimentation.

(B), (C) and (E) A polypeptide which is encoded by a nucleic acid molecule of at least 150 nucleotides in length, or a polypeptide which is at least about 50 amino acids in length.

The instant claim language appears to encompass fragments of canine B7-2 proteins. For example, claim 42 recites a protein encoded by a nucleic acid molecule of at least 150 nucleotides that hybridizes to the complement of SEQ ID NOS:9 or 19. Even under high stringency conditions, molecules shorter than the full length sequence are expected to meet this limitation. Further, claims 44, 47, and 62 specifically read on polypeptides which comprise fragments or truncations of SEQ ID NOS:9 or 19.

However, the specification does not appear to have provided sufficient guidance as to which fragments of SEQ ID NO:7 or 17 would share the activity of binding to CTLA4 or CD28 or stimulating T cells (with the exception of a B7-2 variant lacking at least a portion of the transmembrane domain – claim 41). Neither does the specification appear to have provided any working examples of any functional fragments. Thus it would require undue experimentation of the skilled artisan to determine which fragments of SEQ ID NOS:7 and 17 would have the function of the full length molecules.

The term "comprising" in claims 44 and 47 is open ended and extends the nucleic acid molecule to include additional non-disclosed sequences on either or both sides of the disclosed region. As the term "comprising" is applied to sequences other than full length B7-2 sequences, such as an "at least 50 contiguous amino acid region," or "those encoded by a nucleic acid of at least 150 nucleotides," there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various nucleic acids recited in the instant claims.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for binding to CTLA4 or CD28 or for stimulating T cells. Without detailed direction as to which nucleic acid sequences are essential to the function of the encoded polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of nucleic acid sequences encompassed by the instant claims would share the ability to bind to CTLA4 or CD28 or to stimulate T cells of the disclosed polypeptides of SEQ ID NOS:7 or 17, other than the nucleic acids of SEQ ID NOS:9 and 19.

(D) and (F) Percent Identity.

The claims recite a genus of polypeptides having at least about 85% identity, and a genus of nucleotide sequences having at least about 95% identity to reference sequences, but do not disclose which of the respective variants share any testable functional activity, a feature deemed essential to the instant invention. Applicant has disclosed two nucleic acid sequences and two corresponding protein sequences of the canine B7-2 polypeptide, and thus has disclosed only two "variants". In the absence of some structural basis for the function that must be maintained by the members of the genus, the claimed invention is not described in such a way as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Attwood (Science 2000, Vol. 290, pp. 471-473; in particular, second paragraph) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000, Vol. 18, pp. 34-39; in particular, page 34) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Finally, even single amino acid differences can result in drastically altered functions between two costimulatory proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

In view of this unpredictability, the skilled artisan would not reasonably expect a polypeptide having anything less than *100% identity* over *the full length* of SEQ ID NOS:7 or 17 to share the same function as the polypeptides of SEQ ID NOS:7 or 17. The limitation of "binding a CTLA4 or CD28 protein or stimulating T cells" is not seen as providing a requisite guidance because there is insufficient direction as to those essential sequences for the disclosed activities.

Thus the recitation of percent identity language does not allow the skilled artisan to make and use the encoding nucleic acids commensurate in scope with the instant claims without undue experimentation.

As noted supra, the skilled artisan would not reasonably expect a polypeptide having anything less than *100% identity* over *the full length* of SEQ ID NOS:7 or 17 to share the same function as canine B7-2. The limitations of "binding" or "stimulating" are not seen as providing a requisite enablement, because even if the activity is specified, the specific sequences necessary for these properties are still unknown. Thus the teachings set forth in the specification provide no more than a plan or invitation for those skilled in the art to experiment practicing the claimed invention.

(G) Polypeptide which, when administered to an animal, regulates T-cell mediated immune responses in said animal.

The specification discloses the sequences of B7-2 proteins (SEQ ID NOS: 7, 17, 26, 31, an 34) a canine species, *Canis familiaris*. The instant claim encompasses in its breadth a therapeutic composition which regulates T-cell mediated immune responses in any animal, including distant species which possess highly divergent molecules of the immune system.

While it was recognized by those skilled in the art at the time the invention was made that e.g. human B7-2 molecules may regulate responses of human T cells, at least in vitro (see e.g. US Patent No. 6,084,067; see entire document, in particular columns 67 – 69), it was highly unpredictable what, if any, responses would result from combining B7-2 molecules with T cells from other species. For example, Lazetic et al. (J. Biol. Chem., 2002, Vol. 277(41), pp. 38660 – 38668) teach that B7 variants from different mammalian species vary dramatically in their abilities to interact with human CD28 and CTLA-4 molecules (see entire document, especially Figure 2).

In view of the lack of predictability of the art to which the invention pertains, undue experimentation would be required to practice the claimed invention with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed invention, and absent working examples providing evidence which is reasonably predictive that the claimed compositions are effective for regulating T-cell mediated immune responses in animals other than those disclosed in the specification.

Limiting the scope of the claim to recite regulation of T-cell mediated immune response in canines would obviate this rejection.

To summarize, reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

19. Claims 40 – 45, 47 – 48, 51, 52, 60, and 62 – 63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The following ***written description*** rejection is set forth herein.

Applicant is in possession of isolated proteins of SEQ ID NOS:7 and 17, encoded by nucleic acid molecules of SEQ ID NOS:9 and 19, which, when administered to canines, regulates T-cell mediated immune responses in canines.

Applicant is not in possession of any protein which:

(A) constitutes "any homolog" of B7-2, such as containing modifications in which amino acids have been deleted, inserted, inverted, substituted or derivatized, or arise through natural allelic variation or alternative RNA splicing (claims 40, 41, and 51, directed to a B7 protein as read in light of the specification on page 10, paragraph 2, and page 11, paragraph 2);

(B) is encoded by a nucleic acid molecule of at least 150 nucleotides in length that hybridizes under stringent conditions with a nucleic acid of SEQ ID NO:10 or 20 (claims 42 – 43);

(C) is encoded by a nucleic acid molecule comprising at least 150 contiguous nucleotide region identical to a region of SEQ ID NO:9 or 19 (claim 44);

(D) is encoded by a nucleic acid molecule comprising sequence at least 95% identical to SEQ ID NO:9 or 19 (claims 45 and 60);

(E) is at least about 50 amino acids in length, and comprises an at least 50 contiguous amino acid region identical in sequence to SEQ ID NO:7 or 17 (claims 47 and 62); or

(F) comprises an amino acid sequence at least about 85% identical to SEQ ID NO:7 or 17 (claims 48 and 63),

(G) a polypeptide which, when administered to an animal, regulates T-cell mediated immune responses in said animal (claim 51).

The specification does not describe the claimed subject matter in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses two nucleic acid sequences SEQ ID NOS:9 and 19 (and complements SEQ ID NOS:10 and 20), encoding canine B7-2 polypeptides (SEQ ID NOS:7 and 17) with a disclosed activity of binding CTLA4 and CD28 proteins and stimulating T cells in dogs, cats, horses and humans (page 10 and page 49). The instant claims encompass in their breadth *any* homolog or a polypeptide of 50 amino acids, or a polypeptide with at least 85% identity to canine B7-2, or *any* polypeptide encoded by a nucleic acid that hybridizes to SEQ ID NO:10 or 20, including those that comprise a fragment thereof, which, when administered to *any* animal will regulate T-cell mediated immune response.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Regarding the instant claim limitations, the specification does not appear to provide an adequate written description for the following reasons:

(A) Modifications, allelic variants and splice variants.

The instant claim language encompasses modifications of the disclosed sequences, such as amino acid substitutions, deletions, and insertions (claim 40, read in light of the specification on page 10, paragraph 2 and page 11, paragraph 2). Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al (J Cell Biol. 1990, Vol. 111, pp. 2129-2138; in particular, pages 2132 - 2133) show that a conservative replacement of a single "lysine" reside at position 132 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol. 1988, Vol. 8, pp. 1247-1252; in particular, page 1250 and Table 1) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Also, Metzler et al. (Nature Structural Biol. 1997, Vol. 4, pp. 527-531; in particular, pages 728 – 729 and Table 2) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al.: Science, 1990, Vol. 247, pp. 1306-1310; in particular, page 1306, col. 2).

Thus the recitation of a range of possible protein sequence modifications, in the absence of guidance as to the specific nature of modifications resulting in a functional polypeptide, does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The term "allelic variants" encompasses one of several possible naturally occurring alternate forms of a gene occupying a given locus on a chromosome of an organism or a population of organisms. Similarly, a "splice variant" is a reference to a nucleic acid molecule, usually RNA, which is generated by alternative processing of intron sequences in an RNA transcript of B7-L polypeptide. Applicant has not provided sufficient biochemical information (e.g. nucleic acid sequences, etc.) that distinctly identifies the *allelic variants or splice variants* of SEQ ID NOS:9 or 19, other than those set forth in SEQ ID NOS:9 and 19.

It is not sufficient to define a specificity by its principal biological activity or structure, e.g. for allelic variants or splice variants of SEQ ID NOS:9 and 19, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. The specification appears to provide insufficient description of the structure of allelic variants or splice variants of SEQ ID NOS:9 or 19.

Thus, applicant has not provided sufficient description to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of allelic variants or splice variants of SEQ ID NOS:9 or 19. The scope of the claims must bear a reasonable correlation with the scope of the written description. The specification does not provide for sufficient written description for allelic variants or splice variants of SEQ ID NOS:9 or 19 other than that defined by SEQ ID NOS:9 and 19.

(B) Hybridization.

Similarly, the fact that two nucleic acid sequences will hybridize under stringent conditions (claim 42) does not in and of itself require that the two sequences share any functional activity. It was well known in the art at the time the invention was made that hybridization could occur between two sequence based upon short stretches of 100% identity. Thus a great deal of sequence variability *with respect to the full-length nucleic acid* is possible. Finally, hybridization under conditions other than high stringency would be expected to permit a great deal of variation between the two hybridizing sequences, making it even more unpredictable that the two sequences would share the same function.

Thus hybridization language or limitations regarding either the hybridization conditions or the sequence length over which the hybridization takes place, does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(B), (C) and (E) A polypeptide which is encoded by a nucleic acid molecule of at least 150 nucleotides in length, or a polypeptide which is at least about 50 amino acids in length.

The instant claim language appears to encompass fragments of canine B7-2 proteins. For example, claim 42 recites a protein encoded by a nucleic acid molecule of at least 150 nucleotides that hybridizes to the complement of SEQ ID NOS:9 or 19. Even under high stringency conditions, molecules shorter than the full length sequence are expected to meet this limitation. Further, claims 44, 47, and 62 specifically read on polypeptides which comprise fragments or truncations of SEQ ID NOS:9 or 19.

However, the specification does not appear to have provided sufficient guidance as to which fragments of SEQ ID NO:7 or 17 would share the activity of binding to CTLA4 or CD28 or stimulating T cells (with the exception of a B7-2 variant lacking at least a portion of the transmembrane domain – claim 41). Neither does the specification appear to have provided any working examples of any functional fragments. Thus the inventor(s), at the time the application was filed, do not have possession of the claimed invention, other than the isolated proteins of SEQ ID NOS:7 or 17.

The term "comprising" in claims 44 and 47 is open ended and extends the nucleic acid molecule to include additional non-disclosed sequences on either or both sides of the disclosed region. As the term "comprising" is applied to sequences other than full length B7-2 sequences, such as an "at least 50 contiguous amino acid region," or "those encoded by a nucleic acid of at least 150 nucleotides," there does not appear to be sufficient description in the specification as filed to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for binding to CTLA4 or CD28 or for stimulating T cells. Without detailed direction as to which nucleic acid sequences are essential to the function of the encoded polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of nucleic acid sequences encompassed by the instant claims would share the ability to bind to CTLA4 or CD28 or to stimulate T cells of the disclosed polypeptides of SEQ ID NOS:7 or 17, other than the nucleic acids of SEQ ID NOS:9 and 19.

Thus the written description of the invention fails to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the fragments of canine B7-2 of the claimed invention.

(D) and (F) Percent Identity.

The claims recite a genus of polypeptides having at least about 85% identity, and a genus of nucleotide sequences having at least about 95% identity to reference sequences, but do not disclose which of the respective variants share any testable functional activity, a feature deemed essential to the instant invention. Applicant has disclosed two nucleic acid sequences and two corresponding protein sequences of the canine B7-2 polypeptide, and thus has disclosed only two "variants". In the absence of some structural basis for the function that must be maintained by the members of the genus, the claimed invention is not described in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Attwood (Science 2000, Vol. 290, pp. 471-473; in particular, second paragraph) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000, Vol. 18, pp. 34-39; in particular, page 34) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Finally, even single amino acid differences can result in drastically altered functions between two costimulatory proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus there is insufficient written description to convey to a skilled artisan which if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

Given the absence of sufficient number of working examples of species that share the disclosed functional activities and have less than 100% identity over the full length of the sequence set forth in SEQ ID NO:7 or 17, the skilled artisan would not reasonably expect a polypeptide having anything less than *100% identity* over *the full length* of SEQ ID NOS:7 or 17 to share the same function as the polypeptides of SEQ ID NOS:7 or 17. The limitation of "binding a CTLA4 or CD28 protein or stimulating T cells" is not seen as providing a requisite description of functional activity for the polypeptide because there is insufficient written description to direct the skilled artisan as to those essential sequences for the disclosed activities.

Thus the recitation of percent identity language does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(G) Polypeptide which, when administered to an animal, regulates T-cell mediated immune responses in said animal.

The specification discloses the sequences of B7-2 proteins (SEQ ID NOS: 7, 17, 26, 31, an 34) from only two mammalian species, *Canis familiaris* and *Felis catus*. The instant claim encompasses in its breadth a therapeutic composition which regulates T-cell mediated immune responses in any animal, including distant species which possess highly divergent molecules of the immune system.

While it was recognized by those skilled in the art at the time the invention was made that e.g. human B7-2 molecules may regulate responses of human T cells, at least in vitro (see e.g. US Patent No. 6,084,067; see entire document, in particular columns 67 – 69), it was insufficient information as to what, if any, responses would result from combining B7-2 molecules with T cells from other species. For example, Lazetic et al. (J. Biol. Chem., 2002, Vol. 277(41), pp. 38660 – 38668) teach that B7 variants from different mammalian species vary dramatically in their abilities to interact with human CD28 and CTLA-4 molecules (see entire document, especially Figure 2).

Thus in the absence of a specific and detailed description in applicant's specification of how to effectively practice the claimed invention, and in the absence of working examples providing evidence which is reasonably predictive that the claimed compositions are effective for regulating T-cell mediated immune responses in animals other than those disclosed in the specification, the inventor(s), at the time the application was filed, did not have possession of the claimed invention, other than the composition which, when administered to canines, regulates T-cell mediated immune responses in canines

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

The specification therefore fails to provide an adequate written description of the above noted claim limitations. The skilled artisan would not reasonably expect a polypeptide having anything less than *100% identity* over *the full length* of SEQ ID NO:7 or 17 to share the same function as canine B7-2, or to regulate immune responses in animals other than canines. The limitations of "binding" or "stimulating" are not seen as providing a requisite written description, because the specific sequences necessary for these properties are still unknown. Even though the specification describes how to test the variant nucleic acid sequences to determine whether they encode functional polypeptides, it does not set forth any procedure that will necessarily lead to discovery of such sequences, nor does it even identify any particular example of such variant sequences.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

20. The following is a quotation of the appropriate paragraphs of ***35 U.S.C. 102*** that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

*(**a**) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.*

*(**b**) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

*(**e2**) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 37(c) of this title before the invention thereof by the applicant for patent.*

21. Claims 40, 42, 43, 47 – 52, and 62 – 64 are rejected under 35 U.S.C. **102(a)** as being anticipated by Pinelli et al. (Immunology, 1997 (Dec.), Vol. 92, No. Suppl. 1, p. 39).

Pinelli et al. teach "B7 costimulatory molecules" expressed on macrophages isolated from beagle dogs. The art-recognized definition of B7 costimulatory molecules includes both B7-1 and B7-2 costimulatory proteins, and the use of the word "molecules" in plural by Pinelli et al. demonstrates that both B7-1 and B7-2 costimulatory molecules were included in the teachings. Since B7-1 and B7-2 molecules do not exist in complex with each other, each type of molecule must be present separately on isolated macrophages taught by Pinelli et al. Thus the canine B7-2 protein is inherent in the teachings of Pinelli et al. The B7 protein taught by Pinelli et al. is present on isolated macrophages, it meets the limitation "isolated protein," especially since the claim limitations do not require the protein to be purified.

Claim 42 is included because as the instantly claimed canine B7-2 protein is the same as taught by Pinelli et al., it is the inherent property of the nucleic acids encoding two identical proteins to hybridize to each other under stringent conditions.

Claim 43 is included because as the instantly claimed canine B7-2 protein is the same as taught by Pinelli et al., it is its inherent property to be capable of binding a CTLA4 or CD28 protein or of stimulating T-cells.

Claims 47 – 50 and 62 – 64 are included because as the instantly claimed canine B7-2 protein is the same as taught by Pinelli et al., it is its inherent property to comprise the same amino acid sequence.

Claim 51 is included because the isolated cells expressing B7 molecules, as taught by Pinelli et al., meet the limitation of therapeutic composition comprising B7-2. Administration of isolated cells expressing therapeutic proteins is well known in the art

as cell-based therapy. The limitation of regulating T-cell mediated immune response in an animal is an inherent property of B7 proteins.

Claim 52 is included because the isolated macrophages taught by Pinelli et al. can serve as a carrier in a therapeutic cimopsition.

The reference teachings thus anticipate the claimed invention.

22. Claims 40, 42, 43, 48, 51, 52, and 63 are rejected under 35 U.S.C. **102(b)** as being anticipated by Maher et al. (J. Immunol., 1996, v. 157 (9), p. 3838 – 3844, see entire document).

Maher et al. teach porcine B7-2 proteins (referred to by an alternative name CD86) (see entire document, especially Figure 2), and expression of these proteins in isolated cultured cells (e.g. Fig. 5). Maher et al. also teach that porcine B7-2 protein is a costimulatory of T cells (Table 1). Porcine B7-2 protein has greater than 80% amino acid identity to the canine B7-2 proteins (see the attached alignments), and thus is encompassed by the limitations of claim 40 as read in light of the specification on pages 10 - 11, including containing modifications in which amino acids have been deleted, inserted, inverted, or substituted. Further, DNA encoding porcine B7-2 has greater than 80% identity to DNA encoding the canine molecules of the instant application, at least over partial sequence lengths (see the attached alignments), and thus meets the limitations of claim 42, specifically hybridization under stringent conditions to SEQ ID NOS 10 and 20 (which are complements of SEQ ID NOS 9 and 19, respectively). As the instant specification discloses on page 14, lines 22 – 25, typically at least about 70% identity is sufficient for hybridization under stringent conditions. The property of B7-2 to costimulate T cells, as taught by Maher et al., anticipates limitations of claim 43, since binding to CD28 protein would be an inherent property of this protein.

Claims 48 and 63 are included because the limitation of "at least about 85%" amino acid identity is anticipated by the greater than 80% identity of the protein taught by Maher et al.

Claim 51 is included because isolated cultured cells expressing B7-2 molecules taught by Maher et al. meet the limitation of a therapeutic composition. Administration of isolated cells expressing therapeutic proteins is well known in the art as cell-based therapy. The limitation of regulating T-cell mediated immune response in an animal is an inherent property of B7-2 proteins.

Claim 52 is included because the isolated culture cells taught by Maher et al. can serve as a carrier in a therapeutic composition.

The reference teachings thus anticipate the claimed invention.

23. Claims 40 – 43 and 51 – 52 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,084,067, as evidenced by the disclosure on pages 10 – 11 and page 14 of the instant specification.

The '067 Patent teaches human B7-2 proteins (see entire document, in particular Figs. 8 and 14). Human B7-2 has over 60% identity to SEQ ID NO:7 of the claimed invention (see attached alignment). The '067 Patent teaches an isolated extracellular domain of a B7-2 protein, i.e. a variant of the protein lacking the transmembrane domain (in particular, column 59, lines 35 – 65, and claim 5). B7-2 proteins taught by the '067 Patent bind CD28 and CTLA4 (in particular, columns 66 – 68), and activate T cells (in particular, column 69 and Table 2). The '067 Patent also teaches that B7-2 protein and compositions thereof are useful for therapeutically regulating immune responses (in particular, columns 33 – 37). Compositions may comprise carrier molecules (in particular, column 32 third paragraph).

Human B7-2 protein has greater than 62.3 % amino acid similarity to the canine B7-2 protein (see the attached alignments), and thus is encompassed by the limitations of claim 40 as read in light of the specification on pages 10 - 11, including containing modifications in which amino acids have been deleted, inserted, inverted, or substituted. Further, DNA encoding human B7-2 has 77.8 % identity to DNA encoding the canine molecules of the instant application, at least over partial sequence lengths (see the attached alignment), and thus meets the limitations of claim 42, specifically hybridization under stringent conditions to SEQ ID NOS 10 and 20 (which are complements of SEQ ID NOS 9 and 19, respectively). As the instant specification discloses on page 14, lines 22 – 25, typically at least about 70% identity is sufficient for hybridization under stringent conditions.

The teachings of the '067 Patent regarding an isolated extracellular domain of B7-2 anticipate the claimed limitations of claim 41; the teachings of B7-2 binding to CTLA4 and CD28 and activation of T cells anticipate the limitations of claim 43; and teachings of B7-2-containing compositions useful for therapeutically regulating immune responses anticipate the limitations of claims 51 – 52.

The reference teachings thus anticipate the claimed invention.

24. The following is a quotation of **35 U.S.C. 103(a)** which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

25. Claims 40 – 43, 47 – 52, and 62 – 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinelli et al. (of record), and further in view of US Patent 6,084,067 (of record).

Pinelli et al. have been discussed, supra.

Pinelli et al. do not specifically teach isolated B7-2 proteins (claim 40), B7-2 proteins lacking at least a portion of the transmembrane domain (claim 41), capable of binding CTLA4 or CD28 or stimulating T-cells (claim 43), encoded by nucleic acids which hybridize to SEQ ID NOS:10 or 20 or are homologous to SEQ ID NOS:9 of 19 (claims 42, 44 – 46, 60, and 61), comprises amino acid sequences homologous to SEQ ID NOS:7 or 17 (claims 47 – 50 and 62 – 64). Pinelli et al. do not specifically teach a therapeutic composition comprising a B7-2 protein which, when administered to an animal, regulates T-cell mediated immune responses in the animal (claims 51 – 52).

The '067 Patent has been discussed supra. The Patent teaches isolated human B7-2 proteins (see entire document, in particular, Figs. 8 and 14); an isolated extracellular domain of B7-2 protein, i.e. a variant of the protein lacking the transmembrane domain (in particular, column 59, lines 35 – 65, and claim 5); binding of B7-2 proteins to CD28 and CTLA4 (in particular, columns 66 – 68), and activation of T cells (in particular, column 69 and Table 2). The '067 Patent also teaches that B7-2

protein and compositions thereof are useful for therapeutically regulating immune responses (in particular, columns 33 – 37), and that compositions may comprise carrier molecules (in particular, column 32 third paragraph).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of the '067 Patent to those of Pinelli et al. to obtain the claimed invention.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because canine B7 costimulatory molecules, including B7-2 proteins, as taught by Pinelli et al., would be expected to therapeutically regulate immune responses in canines, as taught by the '067 Patent for human B7-2 proteins which can be used to therapeutically regulate immune responses in humans. One of ordinary skill in the art would have been motivated to incorporate these proteins into therapeutic compositions including a carrier, since the '067 Patent teaches that such compositions can be used to therapeutically regulate immune responses. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

26. Claims 46 and 61 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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August 13, 2004